SHORT RESEARCH ARTICLE

Rapid doubling of Alzheimer's amyloid-β40 and 42 levels in brains of mice exposed to a nickel nanoparticle model of air pollution [v1; ref status: indexed, http://f1000r.es/T5Rxeo]

Soong Ho Kim[1], Elysse M Knight[1], Eric L Saunders[2], Azita K Cuevas[2], Marusia Popovech[2], Lung-Chi Chen[2], Sam Gandy[1,3,4]

[1]Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
[2]Department of Environmental Sciences, New York University, Tuxedo Park, New York, NY 10987, USA
[3]Department of Psychiatry and Alzheimer's Disease Research Center, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
[4]James J. Peters Veterans Affairs Medical Center, Bronx, New York, NY 10468, USA

v1 **First Published:** 21 Dec 2012, **1**:70 (doi: 10.12688/f1000research.1-70.v1)
Latest Published: 21 Dec 2012, **1**:70 (doi: 10.12688/f1000research.1-70.v1)

Abstract

Background: Over 20 genetic risk factors have been confirmed to associate with elevated risk for Alzheimer's disease (AD), but the identification of environmental and/or acquired risk factors has been more elusive. At present, recognized acquired risks for AD include traumatic brain injury, hypercholesterolemia, obesity, hypertension, and type 2 diabetes.
Methods: Based on reports associating various inhalants with AD pathology, we investigated the possibility that air pollution might contribute to AD risk by exposing wild-type mice to a standard air pollution modeling system employing nickel nanoparticle-enriched atmosphere for 3 hr.
Results: Mice exposed to air pollution showed 72-129% increases in brain levels of both amyloid-β peptides Aβ40 and Aβ42, as well as Aβ42/40 ($p < 0.01$).
Conclusions: These effects on elevation of brain Aβ exceed those associated with trisomy 21, a known risk for early onset AD pathology, raising the possibility that clinical importance might be attached. Further work is required to establish the molecular and physiological basis for these phenomena. The rapid, dramatic effect, if verified, would suggest that inhalant exposures should be evaluated for their possible roles in contributing to the environmental risk for common forms of AD.

Article Status Summary

Referee Responses

Referees	1	2	3
v1 published 21 Dec 2012	✓ report	✓ report	✓ report

1 **W Sue Griffin**, University of Arkansas for Medical Sciences USA

2 **George Perry**, University of Texas at San Antonio USA

3 **Ottavio Arancio**, Columbia University Medical Center USA

Latest Comments

No Comments Yet

Corresponding author: Sam Gandy (samuel.gandy@mssm.edu)

How to cite this article: Kim SH, Knight EM, Saunders EL *et al.* (2012) Rapid doubling of Alzheimer's amyloid-β40 and 42 levels in brains of mice exposed to a nickel nanoparticle model of air pollution [v1; ref status: indexed, http://f1000r.es/T5Rxeo] *F1000Research* 2012, **1**:70 (doi: 10.12688/f1000research.1-70.v1)

Grant information: This work was supported by the Cure Alzheimer's Fund (S.G.), VA MERIT Review Award I01BX000348 (S.G.), and the American Health Assistance Foundation A2012625 (S.H.K.). This work was also supported by National Institutes of Health Grant U01ES020126 and P30ES00260 (L.C.C.).
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests:
S.G. holds research grant support from Amicus Pharmaceuticals and Baxter Pharmaceuticals; he is a consultant to Balance Pharmaceuticals and Diagenic; and he is a member of the Data and Safety Monitoring Board for the Pfizer-Janssen Alzheimer's Immunotherapy Alliance.

First Published: 21 Dec 2012, **1**:70 (doi: 10.12688/f1000research.1-70.v1)
First Indexed: 23 Jan 2013, **1**:70 (doi: 10.12688/f1000research.1-70.v1)

Introduction

One common neurodegenerative disease, Parkinson's disease, has been linked to exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and to inhaled manganese[1,2]. Similarly, inhaled aluminum dust has been associated with neurotoxic effects and preclinical cognitive impairment[3]. Certain inhalation anesthetics have also been implicated in elevating AD risk, possibly by exacerbating the neurotoxic oligomerization of the amyloid-β (Aβ) peptide[4]. The early involvement of the olfactory cortex in AD has caused long-time speculation that some inhaled agent might play a role in AD risk[5].

Recently, AD pathology was identified in young people living in areas with high levels of air pollution[6,7]. Furthermore, impaired cognition has been recently attributed to air pollution exposure in some populations[8]. These converging lines of evidence led us to analyze brain levels of Aβ40 and Aβ42 in mice exposed to an inhaled particulate matter (nickel nanoparticle; Ni NP) model of air pollution.

Methods

All procedures involving animals were conducted in compliance with guidelines for ethical animal research and approved by the New York University School of Medicine Animal Care and Use Committee. Two-month-old male and female FVBN mice (Taconic Farm, Hudson, NY) were randomly assigned to Ni NP inhalation (count median diameter 54 nm, at 1 mg/m^3, which is the current Occupational Safety and Health Administration's Permissible Exposure Limit for nickel hydroxide [http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=9992]) (n = 16 per group) or control filtered air (n = 5 per group) for 3 hours in a nose-only exposure chamber. This protocol has been established as a model for air pollution toxicity in pulmonary disease[9], atherosclerosis[10], and insulin resistance[11]. Twenty-four hours post exposure, mice were given pentobarbital, bled out via the vena cava, and then their brains were harvested, snap frozen and stored at -80ºC until assay. For measurement of endogenous mouse brain Aβ40 and Aβ42, we employed the Schmidt method[12] and human/rat Aβ 1–40/1–42 ELISA kits (Wako, Richmond, VA). Statistical analysis was performed via Mann-Whitney test. #8 Ni NP is excluded from the analysis due to being more than 2 SD's away from mean or closest value.

Results

Both endogenous Aβ40 and Aβ42 were elevated in the brains of mice following Ni NP exposure (Figure 1). Aβ 40 was increased by 1.72-fold (P = 0.0011, Mann-Whitney test), and Aβ42 was increased by 2.29-fold (P = 0.0005, Mann-Whitney test). Aβ42/40 ratio was also increased in the Ni NP-exposed group compared to the filtered air control group (0.27 ± 0.01 and 0.21 ± 0.007, respectively; P = 0.0093, Mann-Whitney test). Both male and female mice responded similarly to Ni NP exposure (male *vs*. female for Aβ40 and Aβ42 levels; P > 0.1, Mann-Whitney test).

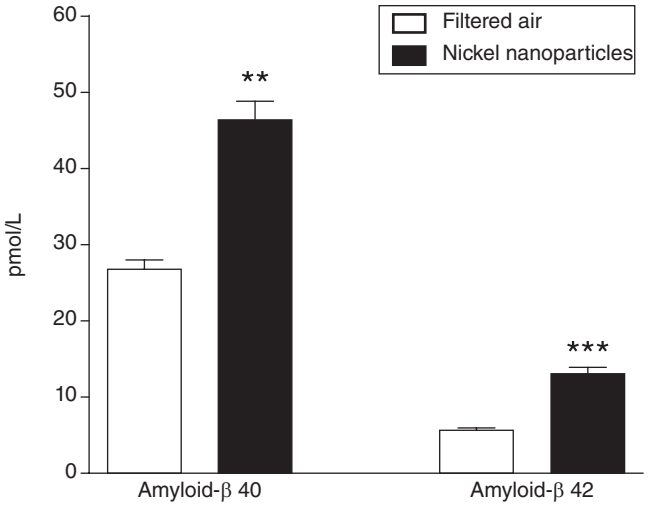

Figure 1. Exposure to air pollution increases amyloid-β (Aβ) levels in the mouse brain. Elevated endogenous mouse brain Aβ40 and Aβ42 in mice exposed to nickel nanoparticles (count median diameter 54 nm, at 1 mg/m^3) (n = 16 per group) versus filtered air (n = 5 per group) for 3 hours in a nose-only exposure chamber. Data presented as mean + SEM. $^{**}P < 0.01$, $^{***}P < 0.001$ (Mann-Whitney test).

Raw data table for endogenous mouse brain Aβ40 and Aβ42 levels in mice exposed to nickel nanoparticles versus filtered air

1 Data File

http://dx.doi.org/10.6084/m9.figshare.105158

Discussion

These data add credence to the proposal[4] that one or more inhaled neurotoxin(s) might increase the risk for AD by elevating levels of brain Aβ. We have not identified whether this accumulation occurs at the level(s) of transcription, translation, or post-translational processing. It is tempting to speculate that the well-known links between inhaled toxins and brain inflammation, and other links between brain inflammation and AD established by Griffin and colleagues[13] may underlie these phenomena.

The changes that we observed were dramatic, rapid, and unexpected. Human Aβ is more aggregatable than murine Aβ, making it conceivable that the effect on Aβ levels in human brain could be even greater. While elucidating the genesis and molecular underpinnings will be an important next step, an even more important step will be a rigorous application of environmental toxicology and epidemiology to determine whether the elevated brain Aβ caused in mice by this air pollution model corresponds to any situation of authentic human inhalation exposure that is linked to an increased risk for AD.

Author contributions

S.H.K., E.M.K., E.L.S. and A.K.C. designed the experiments with L.C.C. and S.G. S.H.K., E.L.S., A.K.C. and M.P. performed the experiments. E.M.K. analyzed the data. S.G. wrote the manuscript. All authors commented on the manuscript. L.C.C. and S.G. supervised the project.

Competing interests

S.G. holds research grant support from Amicus Pharmaceuticals and Baxter Pharmaceuticals; he is a consultant to Balance Pharmaceuticals and Diagenic; and he is a member of the Data and Safety Monitoring Board for the Pfizer-Janssen Alzheimer's Immunotherapy Alliance.

Grant information

This work was supported by the Cure Alzheimer's Fund (S.G.), VA MERIT Review Award I01BX000348 (S.G.), and the American Health Assistance Foundation A2012625 (S.H.K.). This work was also supported by National Institutes of Health Grant U01ES020126 and P30ES00260 (L.C.C.).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Langston JW, Ballard P, Tetrud JW, *et al.*: **Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis.** *Science.* 1983; **219**(4587): 979–80.
PubMed Abstract | Publisher Full Text
2. Cotzias GC, Papavasiliou PS, Ginos J, *et al.*: **Metabolic modification of Parkinson's disease and of chronic manganese poisoning.** *Annu Rev Med.* 1971; **22**: 305–326.
PubMed Abstract | Publisher Full Text
3. Meyer-Baron M, Schäper M, Knapp G, *et al.*: **Occupational aluminum exposure: evidence in support of its neurobehavioral impact.** *Neurotoxicology.* 2007; **28**(6): 1068–1078.
PubMed Abstract | Publisher Full Text
4. Xie Z, Xu Z: **General anesthetics and β-amyloid protein.** *Prog Neuropsychopharmacol Biol Psychiatry.* 2012.
PubMed Abstract | Publisher Full Text | Free Full Text
5. Pearson R, Esiri M, Hiorns RW, *et al.*: **Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer disease.** *Proc Natl Acad Sci U S A.* 1985; **82**(13): 4531–4534.
PubMed Abstract | Publisher Full Text | Free Full Text
6. Calderon-Garciduenas L, Reed W, Maronpot RR, *et al.*: **Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution.** *Toxicol Pathol.* 2004; **32**(6): 650–658.
PubMed Abstract | Publisher Full Text
7. Calderón-Garcidueñas L, Kavanaugh M, Block M, *et al.*: **Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques, and down-regulation of the cellular prion protein in air pollution exposed children and young adults.** *J Alzheimers Dis.* 2012; **28**(1): 93–107.
PubMed Abstract | Publisher Full Text
8. Weuve J, Puett RC, Schwartz J: **Exposure to particulate air pollution and cognitive decline in older women.** *Arch Intern Med.* 2012; **172**(3): 219–227.
PubMed Abstract | Publisher Full Text | Free Full Text
9. Gillespie P, Kang GS, Elder A, *et al.*: **Pulmonary response after exposure to inhaled nickel hydroxide nanoparticles: short and long-term studies in mice.** *Nanotoxicology.* 2010; **4**(1): 106–119.
PubMed Abstract | Publisher Full Text | Free Full Text
10. Kang G, Gillespie PA, Gunnison A, *et al.*: **Long-term inhalation exposure to nickel nanoparticles exacerbated atherosclerosis in a susceptible mouse model.** *Environ Health Perspect.* 2011; **119**: 176–181.
PubMed Abstract | Publisher Full Text | Free Full Text
11. Xu X, Liu C, Xu Z, *et al.*: **Long-term exposure to ambient fine particulate pollution induces insulin resistance and mitochondrial alteration in adipose tissue.** *Toxicol Sci.* 2011; **124**(1): 88–98.
PubMed Abstract | Publisher Full Text | Free Full Text
12. Schmidt S, Jiang Y, Nixon R, *et al.*: **Tissue processing prior to protein analysis and amyloid-beta quantitation.** *Methods Mol Biol.* 2005; **299**: 267–278.
PubMed Abstract | Publisher Full Text
13. Griffin WS, Sheng JG, Royston MC, *et al.*: **Glial-neuronal interactions in Alzheimer's disease: the potential role of a 'cytokine cycle' in disease progression.** *Brain Pathol.* 1998; **8**(1): 65–72.
PubMed Abstract | Publisher Full Text

Current Referee Status:

Referee Responses for Version 1

Ottavio Arancio
Columbia University Medical Center, New York, NY, USA

Approved: 25 January 2013

Referee Report: 25 January 2013
This is an intriguing observation that might potentially have important relevance to the etiopathogenesis of Alzheimer's Disease.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

George Perry
University of Texas at San Antonio, San Antonio, TX, USA

Approved: 23 January 2013

Referee Report: 23 January 2013
Linkage of environmental air toxicity from nanoparticles leading to Alzheimer-like changes in the brain of mice opens a new avenue to understanding the development of brain diseases. These findings are consistent with prior work showing particulate air pollution can affect the brains of human as well as dogs living in polluted cities.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

W Sue Griffin
Department of Geriatrics, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Approved: 21 January 2013

Referee Report: 21 January 2013
Neurodegenerative consequences are a looming possibility with the current increased burden of air-borne pollutants. Many studies have suggested an association between anesthesia administered to older adults and cognitive decline and development or progression of Alzheimer's disease (AD). A number of studies have already established links between air-borne pollutants and risk for development of systemic disorders several of which, like AD are inflammatory in nature. Gandy and his colleagues have taken a

purposeful step toward more directly connecting air-pollution to increased risk for development of AD in a study of wild type mice exposed to a toxin at the OSHA permissible level for an 8h human exposure. The results are very convincing, showing that a one-time 3h exposure to nickel hydroxide nanoparticles at the "permissible" level doubled brain levels of Aβ40 and Aβ42 within 24h—increases that are similar to levels reported in younger adults with Down's syndrome. Interestingly, as noted by the authors, and in accord with systemic inflammatory consequences reported following exposure to air-borne pollutants, neuroinflammatory changes that drive Alzheimer neuropathological change may also be elicited by such exposure. This may be particularly important as we necessarily inhale air that appears to be "clean," but which contains permissible levels of agents that may have adverse effects on the brain, especially in persons with genetic risk factors and or co-morbid conditions that already predispose them for development of AD.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.